5-MEMBERED HETEROCYCLES FOR USE AS ANTIVIRAL AGENTS

10/502383

The invention relates to 5-membered heterocycles and process for their preparation, and to their use for producing medicaments for the treatment and/or prophylaxis of diseases, in particular for use as antiviral agents, in particular against cytomegaloviruses.

EP-A-8391 describes benzimidazole-substituted pyridazinones for cardiovascular disorders and having an antiviral action.

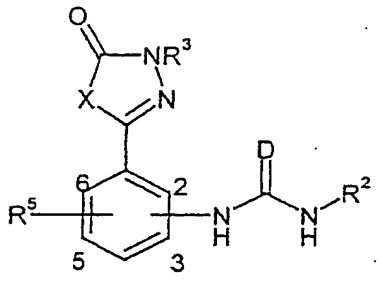
The synthesis of diaryl-1,2,4-(4H)-triazol-5-ones is described in P. Hewawasam et al., Bioorg. Med. Chem. Lett. 2002, 12, 1117-1120.

Although agents with antiviral activity and a different structure are available on the market, it is always possible for resistance to develop. Novel agents for better and effective therapy are therefore desirable.

One object of the present invention is therefore to provide novel compounds having the same or improved antiviral effect for the treatment of viral diseases in humans and animals.

It has been found, surprisingly, that the 5-membered heterocycles described in the present invention have high antiviral activity.

The present invention relates to compounds of the formula

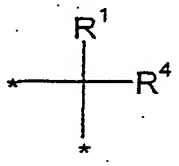


(I)

in which

the radical $-NHC(D)NHR^2$ is bonded to the aromatic system at one of positions 2, 3, 5 or 6,

X is $-N(R^6)-$ or a group



D is oxygen or sulfur,

R^1 is C_6-C_{10}-aryl or C_1-C_6-alkyl, where alkyl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl and C_1-C_6-alkylaminocarbonyl,

and

where aryl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of halogen, hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylaminocarbonyl and C_1-C_6-alkyl,

or

R^1 and R^4 form together with the carbon atom to which they are bonded a C_3-C_6-cycloalkyl ring, where the cycloalkyl ring may optionally be substituted by

up to three substituents independently of one another selected from the group consisting of halogen, hydroxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl and C_1-C_6-alkylaminocarbonyl,

R^2 is C_3-C_8-cycloalkyl or C_6-C_{10}-aryl, where aryl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of halogen, hydroxy, nitro, cyano, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, C_1-C_6-alkylaminocarbonyl and C_1-C_6-alkyl,

R^3 is hydrogen or C_1-C_6-alkyl, where alkyl may optionally be substituted by up to two substituents independently of one another selected from the group consisting of C_1-C_6-alkoxy, hydroxycarbonyl and C_1-C_6-alkoxycarbonyl,

R^4 is C_1-C_6-alkyl, where alkyl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of hydroxy, C_6-C_{10}-aryl, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl and C_1-C_6-alkylaminocarbonyl,

or

R^4 is C_6-C_{10}-aryl, where aryl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of halogen, hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylaminocarbonyl and C_1-C_6-alkyl,

R^5 is hydrogen, halogen, hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino or C_1-C_6-alkyl,

R^6 is C_6-C_{10}-aryl, C_3-C_8-cycloalkyl or C_1-C_6-alkyl, where alkyl may optionally be substituted by up to two substituents independently of one another selected from the group consisting of hydroxy, C_6-C_{10}-aryl, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, hydroxycarbonyl and C_1-C_6-alkoxycarbonyl,

and

where cycloalkyl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of hydroxy, C_1-C_6-alkyl, C_6-C_{10}-aryl, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, hydroxycarbonyl and C_1-C_6-alkoxycarbonyl.

The compounds of the invention may also be in the form of their salts, solvates or solvates of the salts.

The compounds of the invention may, depending on their structure, exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore relates to the enantiomers or diastereomers and respective mixtures thereof. The stereoisomerically pure constituents can be isolated in a known manner from such mixtures of enantiomers and/or diastereomers.

The invention also relates, depending on the structure of the compounds, to tautomers of the compounds.

Salts which are preferred for the purposes of the invention are physiologically acceptable salts of the compounds of the invention.

Physiologically acceptable salts of the compounds (I) include acid addition salts of mineral acids, carboxylic acids and sulfonic acids, i.e. salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds (I) also include salts of usual bases such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 C atoms such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, dihydroabiethylamine, arginine, lysine, ethylenediamine and methylpiperidine.

Solvates refer for the purposes of the invention to those forms of the compounds which form a complex in the solid or liquid state by coordination with solvent molecules. Hydrates are a special form of solvates in which the coordination takes place with water.

For the purposes of the present invention, unless specified otherwise, the substituents have the following meaning:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylamino, alkylaminocarbonyl and alkoxycarbonyl are a linear or branched alkyl radical having normally 1 to 6, preferably 1 to 4, particularly preferably 1 to 3, carbon atoms, by way of example and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy is, by way of example and preferably, methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino is an alkylamino radical having one or two alkyl substituents (chosen independently of one another), by way of example and preferably methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-tert-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

Alkylaminocarbonyl is an alkylaminocarbonyl having one or two alkyl substituents (chosen independently of one another), by way of example and preferably methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyll, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-t-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylaminocarbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl.

Alkoxycarbonyl is, by way of example and preferably, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Cycloalkyl is a cycloalkyl group having normally 3 to 8, preferably 5 to 7, carbon atoms, by way of example and preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl.

Aryl is a mono- to tricyclic aromatic carbocyclic radical having normally 6 to 14 carbon atoms, by way of example and preferably phenyl, naphthyl and phenanthrenyl.

Heterocyclyl is a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having normally 4 to 10, preferably 5 to 8, ring atoms and up to 3, preferably up to 2, heteroatoms and/or hetero groups from the series N, O, S, SO, SO_2. The heterocyclyl radicals may be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two heteroatoms from the series O, N and S, such as, by way of example and preferably, tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

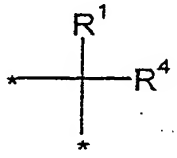
Halogen is fluorine, chlorine, bromine and iodine, preferably fluorine and chlorine.

Preferred compounds of the formula (I) are those

in which

the radical $-NHC(D)NHR^2$ is bonded to the aromatic system at one of positions 2, 3, 5 or 6,

X is $-N(R^6)-$ or a group



D is oxygen,

R^1 is C_1-C_6-alkyl, where alkyl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl and C_1-C_6-alkylaminocarbonyl,

or

R^1 and R^4 form together with the carbon atom to which they are bonded a C_5-C_6-cycloalkyl ring, where the cycloalkyl ring may optionally be substituted by up to three substituents independently of one another selected from the group consisting of halogen, hydroxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl and C_1-C_6-alkylaminocarbonyl,

R^2 is C_6-C_{10}-aryl, where aryl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of halogen or C_1-C_6-alkyl,

R^3 is hydrogen or C_1-C_6-alkyl, where alkyl may optionally be substituted by up to two substituents independently of one another selected from the group consisting of C_1-C_6-alkoxy, hydroxycarbonyl and C_1-C_6-alkoxycarbonyl,

R^4 is C_1-C_6-alkyl, where alkyl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of hydroxy, phenyl, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl and C_1-C_6-alkylaminocarbonyl,

R^5 is hydrogen, halogen, hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino or C_1-C_6-alkyl,

R^6 is C_3-C_8-cycloalkyl or C_1-C_6-alkyl, where alkyl may optionally be substituted by up to two substituents independently of one another selected from the group consisting of hydroxy, C_6-C_{10}-aryl, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, hydroxycarbonyl and C_1-C_6-alkoxycarbonyl,

and

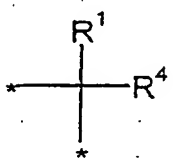
where cycloalkyl may optionally be substituted by up to three substituents independently of one another selected from the group consisting of C_1-C_6-alkyl and C_1-C_6-alkoxy.

Preferred compounds of the formula (I) are also those

in which

the radical $-NHC(D)NHR^2$ is bonded to the aromatic system at position 3,

X is $-N(R^6)-$ or a group



D is oxygen,

R^1 is C_1-C_6-alkyl,

or

R^1 and R^4 form together with the carbon atom to which they are bonded a C_5-C_6-cycloalkyl ring,

R^2 is C_6-C_{10}-aryl, where aryl may optionally be substituted by up to two substituents independently of one another selected from the group consisting of fluorine, chlorine or C_1-C_6-alkyl,

R^3 is hydrogen,

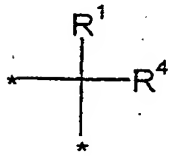
R^4 is C_1-C_6-alkyl,

R^5 is hydrogen or fluorine,

R^6 is C_5-C_7-cycloalkyl or C_1-C_6-alkyl, where alkyl may optionally be substituted by up to two substituents phenyl.

In a further preferred embodiment, the radical $-NHC(D)NHR^2$ in the compounds of the formula (I) is bonded to the aromatic system at position 3.

In a further preferred embodiment, X in the compounds of the formula (I) is a group



In a further preferred embodiment, X in the compounds of the formula (I) is $-N(R^6)-$.

In a further preferred embodiment, the compounds of the formula (I) have oxygen for D.

In a further preferred embodiment, R^1 is methyl, or R^1 and R^4 form together with the carbon atom to which they are bonded a cyclohexyl ring. R^1 is preferably methyl.

In a further preferred embodiment, compounds of the formula (I) have phenyl for R^2, where phenyl may optionally be substituted by up to two substituents independently of one another selected from the group consisting of fluorine, chlorine or methyl.

In a further preferred embodiment, R^3 is hydrogen.

In a further preferred embodiment, R^4 is methyl.

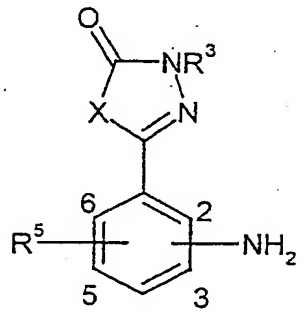
In a further preferred embodiment, R^5 is hydrogen.

In a further preferred embodiment, R^6 is isopropyl, cyclohexyl or 1-phenylethyl.

The definitions of radicals indicated specifically in the respective combinations or preferred combinations of radicals are replaced irrespective of the particular combinations indicated for the radicals as desired also by definitions of radicals of another combination.

Combinations of two or more of the abovementioned preferred ranges are very particularly preferred.

The invention further relates to process for preparing the compounds of the formula (I), characterized in that compounds of the formula (II)



(II),

in which

NH_2 is bonded to the aromatic system at one of positions 2, 3, 5 or 6, and

X, R^3 and R^5 have the meaning indicated above,

are reacted with compounds of the formula (III)

$$DCN\text{-}R^2 \qquad (III)$$

in which R^2 and D have the meaning indicated above.

The reaction takes place in inert solvents, where appropriate in the presence of a base, preferably in a temperature range from room temperature up to reflux of the solvents under atmospheric pressure.

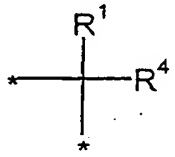
Examples of inert solvents are halohydrocarbons such as methylene chloride, trichloromethane, tetrachloromethane, trichloroethane, tetrachloroethane,

1,2-dichloroethane or trichloroethylene, ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 2-butanone, dimethyl sulfoxide, acetonitrile or pyridine, with preference for tetrahydrofuran or methylene chloride.

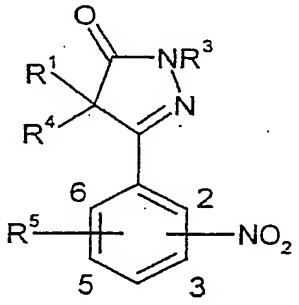
Examples of bases are alkali metal carbonates such as cesium carbonate, sodium or potassium carbonate, or potassium tert-butoxide, or other bases such as sodium hydride, DBU, triethylamine or diisopropylethylamine, with preference for diisopropylethylamine and triethylamine.

The compounds of the formula (III) are known or can be synthesized from the appropriate precursors by known processes.

The compounds of the formula (IIa), which represent compounds of the formula (II) in which X is



can be prepared by reducing the compounds of the formula (IV)



(IV),

in which

NO_2 is bonded to the aromatic system at one of positions 2, 3, 5 or 6, and

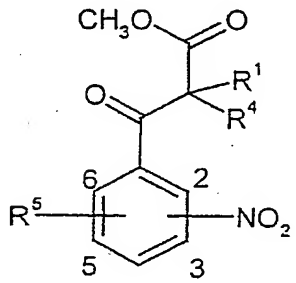
R^1, R^3, R^4 and R^5 have the meaning indicated above,

e.g. with tin(II) chloride or hydrogen with palladium on carbon.

The reaction takes place in inert solvents, preferably in a temperature range from room temperature to reflux of the solvents under atmospheric pressure up to 3 bar.

Examples of inert solvents are ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as dimethylformamide, dimethylacetamide, acetonitrile or pyridine, with preference for ethanol, isopropanol or, in the case of tin dichloride, in dimethylformamide.

The compounds of the formula (IV) can be prepared by reacting compounds of the formula (V)



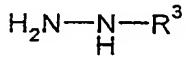
(V),

in which

NO_2 is bonded to the aromatic system at one of positions 2, 3, 5 or 6, and

R^1, R^4 and R^5 have the meaning indicated above,

with hydrazine or a compound of the general formula (VI),



(VI)

in which

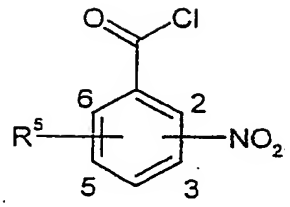
R^3 has the meaning indicated above.

The reaction takes place in inert solvents, preferably in a temperature range from room temperature to reflux of the solvents under atmospheric pressure.

Examples of inert solvents are ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as dimethylformamide, dimethylacetamide, acetonitrile or pyridine, with preference for ethanol or isopropanol.

The compounds of the formula (VI) are known or can be synthesized from the appropriate precursors by known processes.

The compounds of the formula (V) can be prepared by reacting compounds of the formula (VII)



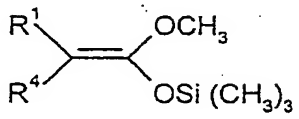
(VII),

in which

NO_2 is bonded to the aromatic system at one of positions 2, 3, 5 or 6, and

R^5 has the meaning indicated above,

with compounds of the formula (VIII)



(VIII)

in which R^1 and R^4 have the meaning indicated above,

in the presence of boron trifluoroetherate.

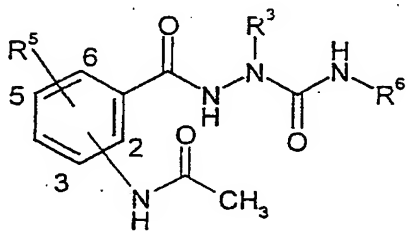
The reaction takes place in inert solvents, preferably in a temperature range from room temperature to reflux of the solvents under atmospheric pressure.

Examples of inert solvents are ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as dimethylacetamide, acetonitrile or pyridine, with preference for diethyl ether.

The compounds of the formula (VII) are known or can be prepared in analogy to known processes.

The compounds of the formula (VIII) are known or can be prepared in analogy to C. Ainsworth, F. Chen, Y.-N. Kuo, *J. Organomet. Chem.* **1972**, *46*, 59-71.

The compounds of the formula (IIb), which represent compounds of the formula (II) in which X is NR^6, can be prepared by reacting compounds of the formula (IX)



(IX),

in which

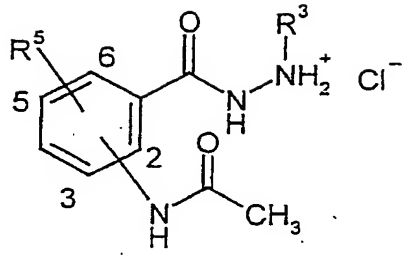
$NHC(O)CH_3$ is bonded to the aromatic system at one of positions 2, 3, 5 or 6, and

R^3, R^5 and R^6 have the meaning indicated above,

in water in the presence of a base, preferably at 60°C to reflux of the water under atmospheric pressure.

Examples of bases are alkali metal hydroxides such as sodium, lithium or potassium hydroxide, alkali metal carbonates such as cesium carbonate, sodium or potassium carbonate, with preference for sodium hydroxide.

The compounds of the formula (IX) can be prepared by reacting compounds of the formula (X)



(X),

in which

$NHC(O)CH_3$ is bonded to the aromatic system at one of positions 2, 3, 5 or 6, and

R^3, R^5 and R^6 have the meaning indicated above,

with compounds of the formula (XI)

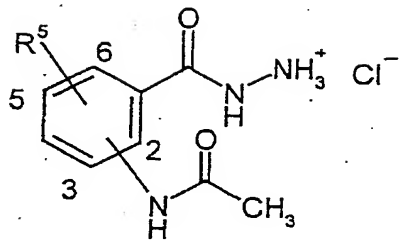
$$OCN—R^6 \qquad (XI)$$

in which R^6 has the meaning indicated above,

by the process described for the preparation of compounds of the formula (I).

The compounds of the formula (XI) are known or can be prepared in analogy to known processes.

The compounds of the formula (X) can be prepared by reacting compounds of the formula (XII)



(XII),

in which

$NHC(O)CH_3$ is bonded to the aromatic system at one of positions 2, 3, 5 or 6, and

R^5 has the meaning indicated above,

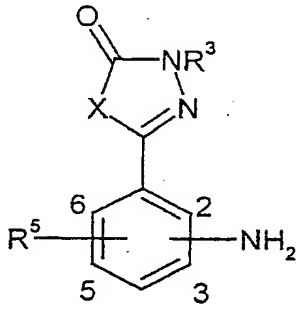
with compounds of the formula (XIII)

$$OHC\text{-}R^3 \qquad (XIII)$$

in a reductive amination by processes known to the skilled worker for reductive aminations.

The compounds of the formulae (XII) and (XIII) are known or can be prepared in analogy to known processes.

Compounds of the formula (II)



(II),

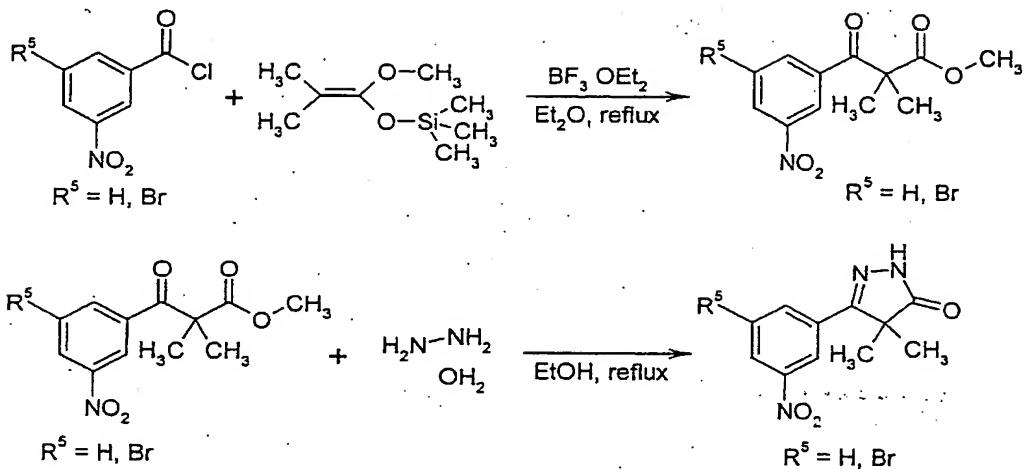
in which

NH_2 is bonded to the aromatic system at one of positions 2, 3, 5 or 6, and

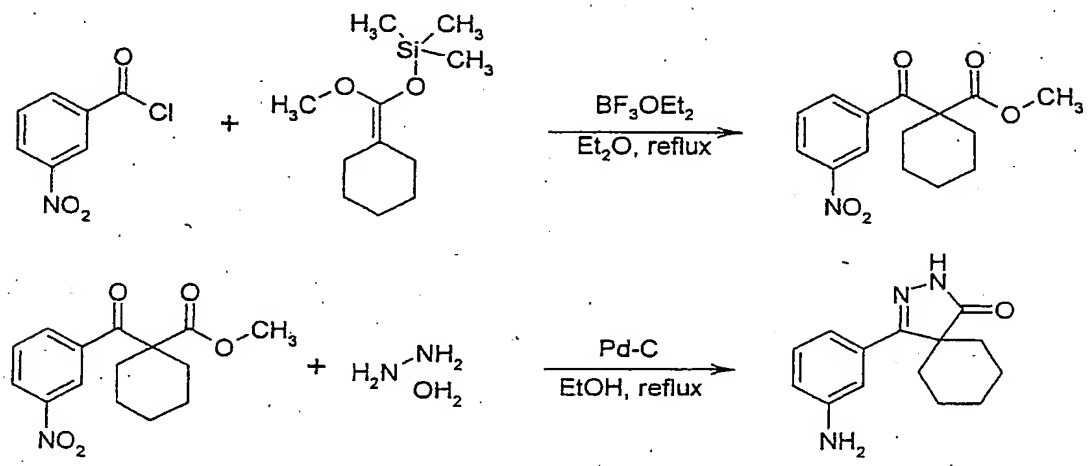
X, R^3 and R^5 have the meaning indicated above, thus represent valuable intermediates, and the present invention therefore likewise relates thereto.

Preparation of the compounds of the invention can be illustrated by the following synthesis schemes 1-8.

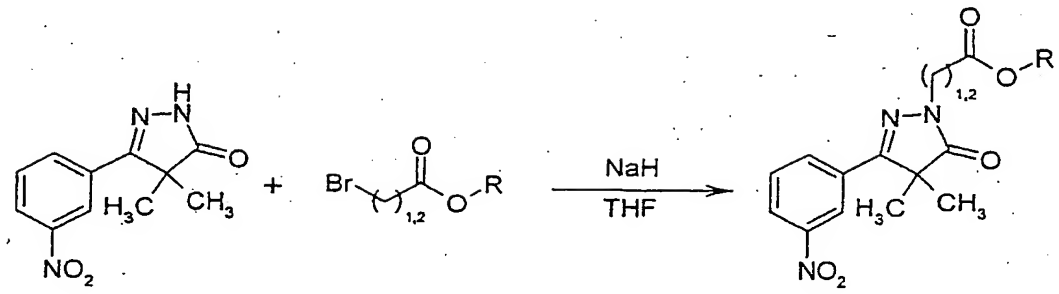
Synthesis schemes:



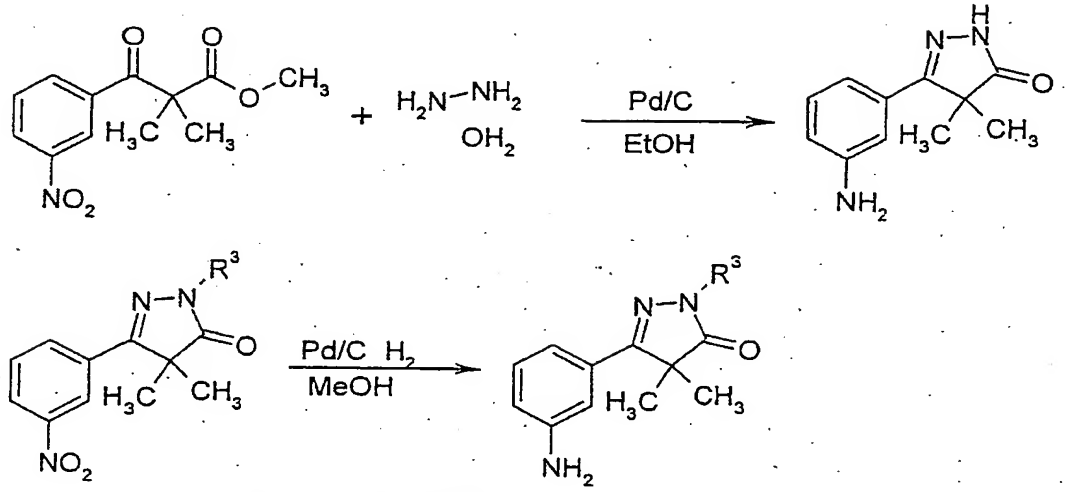
Scheme 1



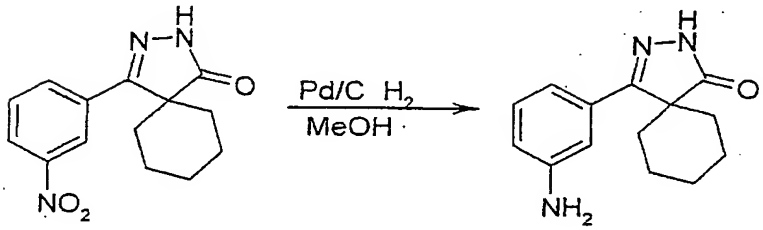
Scheme 2



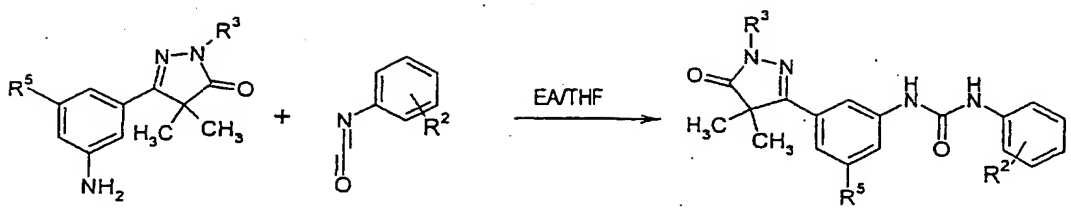
Scheme 3: Alkylation of pyrazolones



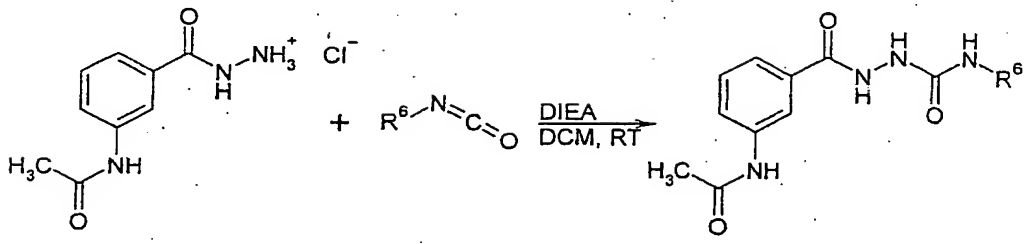
R^1 = H, CH_2COOEt



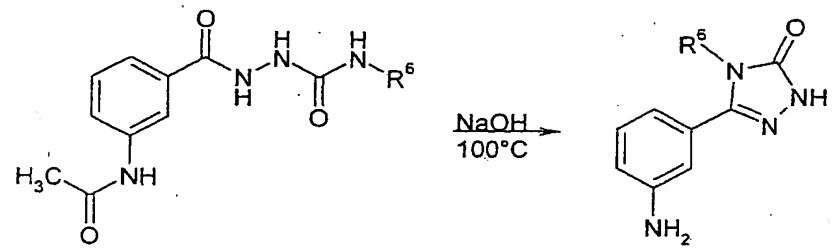
Scheme 4: Reactions to give the aniline



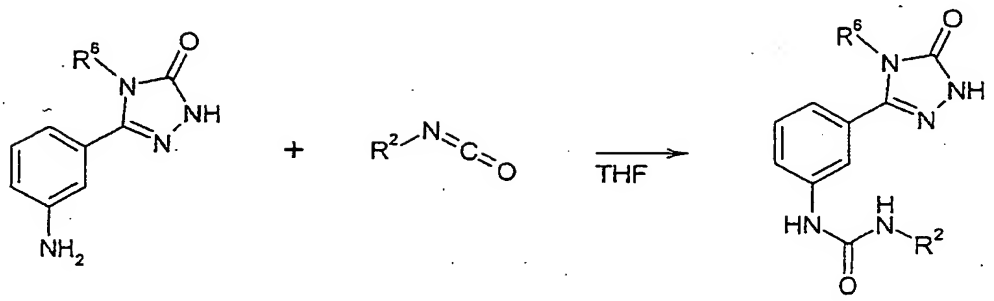
Scheme 5: Urea syntheses



Scheme 6: Synthesis of hydrazinecarboxamides



Scheme 7: Synthesis of 3-aminotriazolonés



Scheme 8: Urea syntheses

The compounds of the invention of the general formula (I) show a surprising range of effects which would not have been predicted. They show an antiviral effect on representatives of the group of herpes viridae, particularly on the human cytomegalovirus (HCMV). They are therefore suitable for the treatment and prophylaxis of diseases caused by herpes viridae, in particular of diseases caused by human cytomegaloviruses.

The compounds of the general formula (I) can, by reason of their particular properties, be used to produce medicaments which are suitable for the prophylaxis or treatment of diseases, especially viral diseases.

The compounds of the invention represent, by reason of their properties, valuable active ingredients for the treatment and prophylaxis of human cytomegalovirus infections and diseases caused thereby. Areas of indication which may be mentioned by way of example are:

1) Treatment and prophylaxis of HCMV infections in AIDS patients (retinitis, pneumonitis, gastrointestinal infections).

2) Treatment and prophylaxis of cytomegalovirus infections in bone-marrow and organ transplant patients who develop often life-threatening HCMV pneumonitis or encephalitis, and gastrointestinal and systemic HCMV infections.

3) Treatment and prophylaxis of HCMV infections in neonates and infants.

4) Treatment of an acute HCMV infection in pregnant women.

5) Treatment of HCMV infection in immunosuppressed patients associated with cancer and cancer therapy.

The novel active ingredients can be employed alone and, if desired, also in combination with other antiviral active ingredients such as, for example, gancyclovir or acyclovir.

The present invention further relates to medicaments which comprise at least one compound of the invention, preferably together with one or more pharmacologically acceptable excipients or carriers, and to the use thereof for the aforementioned purposes.

The active ingredient may be systemic and/or local effects. It can for this purpose be administered in a suitable way, such as, for example, by the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, transdermal, conjunctival or otic route, or as implant.

For these administration routes it is possible to administer the active ingredient in suitable administration forms.

Suitable for oral administration are known administration forms which deliver the active ingredient rapidly and/or in modified manner, such as, for example, tablets (uncoated and coated tablets, e.g. tablets provided with enteric coatings or film-coated tablets), capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, solutions and aerosols.

Parenteral administration can take place with avoidance of an absorption step (intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with inclusion

of absorption (intramuscular, subcutaneous, intracutaneous, percutaneous, or intraperitoneal). Administration forms suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders.

Examples suitable for the other administration routes are pharmaceutical forms for inhalation (inter alia powder inhalers, nebulizers), nasal drops/solutions, sprays; tablets or capsules to be administered lingually, sublingually or buccally, suppositories, preparations for the eyes and ears, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, milk, pastes, dusting powders or implants.

The active ingredients can be converted in a manner known per se into the stated administration forms. This takes place with use of inert, non-toxic, pharmaceutically suitable excipients. These include, inter alia, carriers (for example microcrystalline cellulose), solvents (for example liquid polyethylene glycols), emulsifiers (for example sodium dodecyl sulfate), dispersants (for example polyvinylpyrrolidone), synthetic and natural biopolymers (for example albumin), stabilizers (for example antioxidants such as ascorbic acid), colors (for example inorganic pigments such as iron oxides) or flavor- and/or odor-masking agents.

It has generally proved advantageous to administer on intravenous administration amounts of about 0.001 to 10 mg/kg, preferably about 0.01 to 5 mg/kg, of body weight to achieve effective results, and the dosage on oral administration is about 0.01 to 25 mg/kg, preferably 0.1 to 10 mg/kg, of body weight.

It may nevertheless be necessary where appropriate to deviate from the amounts mentioned, specifically as a function of the body weight, administration route, individual response to the active ingredient, mode of preparation and time or interval over which administration takes place. Thus, it may be sufficient in some cases to make do with less than the aforementioned minimal amount, whereas in other cases the upper limit mentioned must be exceeded. It may in the event of administration of

larger amounts be advisable to divide these into a plurality of individual doses over the day.

The percentage data in the following tests and examples are percentages by weight unless otherwise indicated; parts are parts by weight. Solvent ratios, dilution ratios and concentration data of liquid/liquid solutions are in each case based on volume.

A. Examples

Abbreviations:

DCI	direct chemical ionization (in MS)
DCM	dichloromethane
DIEA	*N,N*-diisopropylethylamine
DMSO	dimethyl sulfoxide
DMF	dimethylformamide
EA	ethyl acetate (acetic acid ethyl ester)
ESI	electrospray ionization (in MS)
h	hour
HPLC	high pressure, high performance liquid chromatography
LC-MS	coupled liquid chromatography-mass spectroscopy
m.p.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
RP-HPLC	reverse phase HPLC
RT	room temperature
R_t	retention time (in HPLC)
THF	tetrahydrofuran
TLC	thin layer chromatography

General LC-MS and HPLC methods:

HPLC parameters:

Method 1: column: Kromasil C18, L-R temperature: 30°C, flow rate = 0.75 $mlmin^{-1}$, eluent: A = 0.01 M $HClO_4$, B = CH_3CN, gradient: → 0.5 min 98%A → 4.5 min 10%A → 6.5 min 10%A

Method 3: column: Kromasil C18 60*2, L-R temperature: 30°C, flow rate = 0.75 $mlmin^{-1}$, eluent: A = 0.005 M $HClO_4$, B = CH_3CN, gradient: → 0.5 min 98%A → 4.5 min 10%A → 6.5 min 10%A

Method 10: LCMS = column: symmetry C18 2.1x150 mm, column oven: 70°C, flow rate = 0.0 $mlmin^{-1}$, eluent: A = CH_3CN, B = 0.23 g of 30% strength HCl/l of water, gradient: 0.0 min 2%A → 2.5 min 95%A → 5.0 min 95%A

Starting compounds

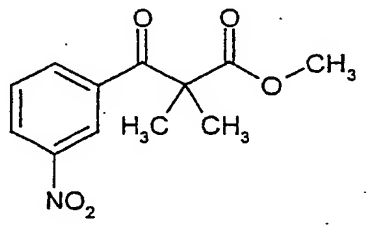
General method 1:

Synthesis of β-keto esters (analogous to the method of M.H. Stefaniak, F. Tinardon, J.D. Wallis, Synlett 1997, 677-678).

1 equivalent of the appropriately substituted 3-nitrobenzoyl chloride are dissolved in absolute diethyl ether (0.25 M solution) in a heat-dried 500 ml three-necked flask under an argon atmosphere, and 1 equivalent of 1-methoxy-2-methyl-1-trimethyl-siloxypropen (C. Ainsworth, F. Chen, Y.-N. Kuo, J. Organomet. Chem. 1972, 46, 59-71) are added. Addition of one equivalent (where appropriate 3 equivalents) of boron trifluoride-diethyl ether complex is followed by heating to reflux for 24 hours. After the reaction mixture has cooled it is washed once each with 1N sodium hydroxide solution, water and saturated brine. The organic phase is dried over magnesium sulfate. Filtration and removal of the solvent was followed by purification of the crude product by column chromatography (silica gel: cyclohexane/ethyl acetate 9:1).

Example 1A

Methyl 2,2-dimethyl-3-(3-nitrophenyl)-3-oxopropanoate



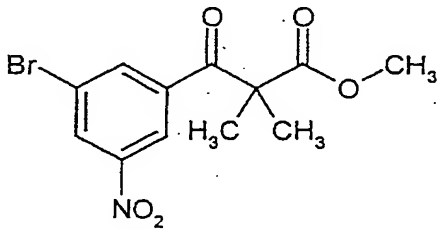
4.93 g (25% of theory) of product are obtained starting from 10 g (53.9 mmol) of 3-nitrobenzoyl chloride with 9.40 g (53.9 mmol) of 1-methoxy-2-methyl-1-trimethylsiloxypropene and 7.65 g (53.9 mmol) of boron trifluoride-diethyl ether complex.

HPLC (method 3): R_t = 4.49 min

MS (DCI): m/z = 269 $(M+NH_4)^+$

Example 2A

Methyl 3-(3-bromo-5-nitrophenyl)-2,2-dimethyl-3-oxopropanoate



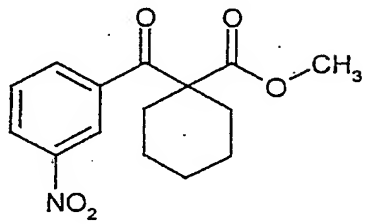
3.62 g (58% of theory) of product are obtained starting from 5 g (18.9 mmol) of 3-bromo-5-nitrobenzoyl chloride with 3.30 g (18.9 mmol) of 1-methoxy-2-methyl-1-trimethylsiloxypropene and 2.68 g (18.9 mmol) of boron trifluoride-diethyl ether complex.

HPLC (method 3): R_t = 4.86 min

MS (DCI): m/z = 347 $(M+NH_4)^+$

Example 3A

Methyl 1-(3-nitrobenzoyl)cyclohexanecarboxylate



0.81 g (28% of theory) of product is obtained starting from 1.84 g (9.92 mmol) of 3-bromo-5-nitrobenzoyl chloride with 2.13 g (9.92 mmol) of [cyclohexylidene-(methoxy)methoxy]trimethylsilane (C. Ainsworth, F. Chen, Y.-N. Kuo, J. Organomet. Chem. 1972, 46, 59-71) and 4.22 g (29.8 mmol) of boron trifluoride-diethyl ether complex.

HPLC (method 3): R_t = 4.90 min

MS (DCI): m/z = 309 $(M+NH_4)^+$

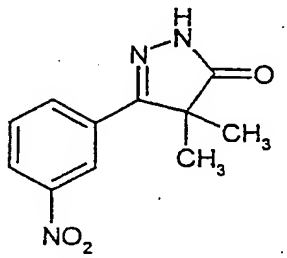
General method 2:

Pyrazolone syntheses

1 equivalent of the β-keto ester is heated to reflux together with 5 equivalents of hydrazine hydrate in ethanol (0.23 M solution) for 4 hours. Either the reaction product separates from the reaction mixture, or it is precipitated with water and cyclohexane after removal of part of the solvent. The precipitate is filtered off with suction, washed with diethyl ether and then dried in vacuo.

Example 4A

4,4-Dimethyl-5-(3-nitrophenyl)-2,4-dihydro-3H-pyrazol-3-one



6.63 g (83% of theory) of product are obtained starting from 8.53 g (34 mmol) of methyl 2,2-dimethyl-3-(3-nitrophenyl)-3-oxopropanoate with 8.50 g (170 mmol) of hydrazine hydrate.

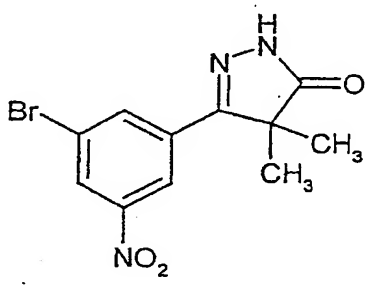
m.p.: 164.6°C

HPLC (method 3): R_t = 3.99 min

MS (DCI): m/z = 251 $(M+NH_4)^+$

Example 5A

5-(3-Bromo-5-nitrophenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one



3.12 g (87% of theory) of product are obtained starting from 3.80 g (11.5 mmol) of methyl 3-(3-bromo-5-nitrophenyl)-2,2-dimethyl-3-oxopropanoate with 2.88 g (57.6 mmol) of hydrazine hydrate.

m.p.: 214.9°C

HPLC (method 3): R_t = 4.26 min

MS (ESIpos): m/z = 312 $(M+H)^+$

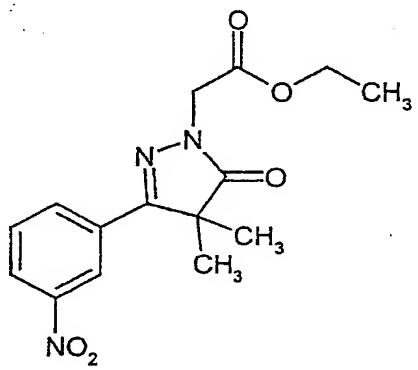
General method 3:

Alkylation of the pyrazolone nitrogen

1 equivalent of the appropriate pyrazolone is dissolved in absolute THF (0.1-0.25 M solution) in a heat-dried flask under an argon atmosphere. After cooling to 0°C, 1.2-1.5 equivalents of sodium hydride are added in portions. The mixture is stirred at room temperature for 30 min and then 1.2-2.5 equivalents of the alkylating agent are added. The reaction mixture is stirred at room temperature overnight and, after cautious addition of water, extracted three times with diethyl ether. The combined organic phases are dried over magnesium sulfate and then filtered and concentrated. The residue is purified by column chromatography.

Example 6A

Ethyl [4,4-dimethyl-3-(3-nitrophenyl)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]acetate



0.82 g (32% of theory) of product is obtained starting from 1.85 g (7.9 mmol) of 4,4-dimethyl-5-(3-nitrophenyl)-2,4-dihydro-3*H*-pyrazol-3-one, after deprotonation with 0.46 g (11.9 mmol) of sodium hydride (60% dispersion in mineral oil), with 1.59 g (9.5 mmol) of ethyl bromoacetate.

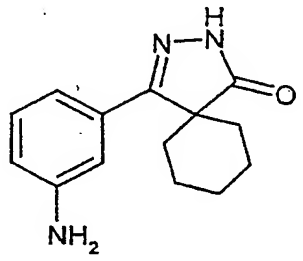
m.p.: 120.2°C

HPLC (method 3): R_t = 4.46 min

MS (DCI): m/z = 320 $(M+NH_4)^+$

Example 7A

4-(3-Aminophenyl)-2,3-diazaspiro[4.5]dec-3-en-1-one



803 mg (2.76 mmol) of methyl 1-(3-nitrobenzoyl)cyclohexanecarboxylate are dissolved in 15 ml of ethanol, and 1.38 g (27.6 mmol) of hydrazine hydrate and 140 mg of palladium on carbon (10%) are added. The mixture is stirred under reflux overnight. The desired product can be precipitated by adding cyclohexane. This results in 278 mg (41% of theory) of product.

HPLC (method 3): R_t = 3.31 min

MS (ESIpos): m/z = 244 $(M+H)^+$

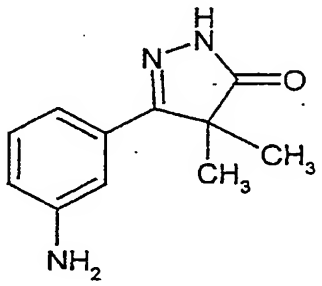
General method 4:

Catalytic hydrogenation of the aromatic nitro group

20 mmol of the substance to be hydrogenated are dissolved in 100 ml of degassed methanol and then, under argon, 250 mg of palladium on activated carbon are added. Hydrogenation is continued under a hydrogen atmosphere (atmospheric pressure) until a TLC check indicates that conversion is complete. The mixture is then filtered with substance through kieselguhr, the filtrate is concentrated, and the residue is dried in vacuo and processed further without further purification.

Example 8A

4,4-Dimethyl-5-(3-aminophenyl)-2,4-dihydro-3*H*-pyrazol-3-one



366 g (91% of theory) of product are obtained starting from 4.60 g (19.2 mmol) of 4,4-dimethyl-5-(3-nitrophenyl)-2,4-dihydro-3*H*-pyrazol-3-one.

HPLC (method 3): R_t = 3.04 min

MS (ESIpos): m/z = 204 $(M+H)^+$

Alternative synthesis of 4,4-dimethyl-5-(3-aminophenyl)-2,4-dihydro-3*H*-pyrazol-3-one:

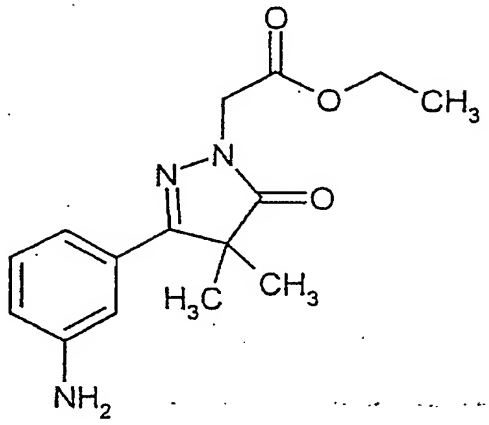
772 mg (2.49 mmol) of methyl 2,2-dimethyl-3-(3-nitrophenyl)-3-oxopropanoate, 1.87 g (37.4 mmol) of hydrazine hydrate are dissolved in 80 ml of ethanol, 100 mg of palladium on activated carbon are added, and the mixture is heated under reflux for 20 hours. It is filtered hot through kieselguhr and washed with ethanol. After most of the ethanol has been removed, cyclohexane and a little water are added, and the mixture is put in a refrigerator. After crystallization is complete, the product is filtered off with suction, washed with diethyl ether and dried in vacuo. 413 mg (82% of theory) of product are obtained.

HPLC (method 3): R_t = 3.03 min

MS (DCI): m/z = 204 $(M+H)^+$

Example 9A

Ethyl [3-(3-aminophenyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]acetate



449 mg (85% of theory) of product are obtained starting from 500 mg (1.57 mmol) of ethyl [4,4-dimethyl-3-(3-nitrophenyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]acetate.

HPLC (method 3): R_t = 3.37 min

MS (EPIpos): m/z = 290 $(M+H)^+$

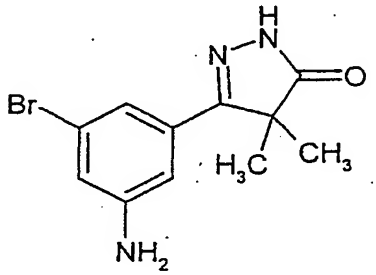
General method 5:

Reduction of the nitro group in bromine-containing aromatic compounds

0.8 mmol of the bromine-containing aromatic nitro compound are dissolved in 10 ml of dioxane and, after addition of 4 mmol of tin chloride dihydrate and a few drops of hydrochloric acid, heated at 70°C for 2 hours. Cooling to room temperature is followed by dilution with ethyl acetate and washing 3 times with 1N sodium hydroxide solution. The organic phase is dried over magnesium sulfate and, after filtration, concentrated. This is followed where appropriate by purification by column chromatography. However, if the purity is appropriate, it is also possible for the crude product which has not been further purified to be processed further.

Example 10A

4,4-Dimethyl-5-(5-amino-3-bromophenyl)-2,4-dihydro-3*H*-pyrazol-3-one



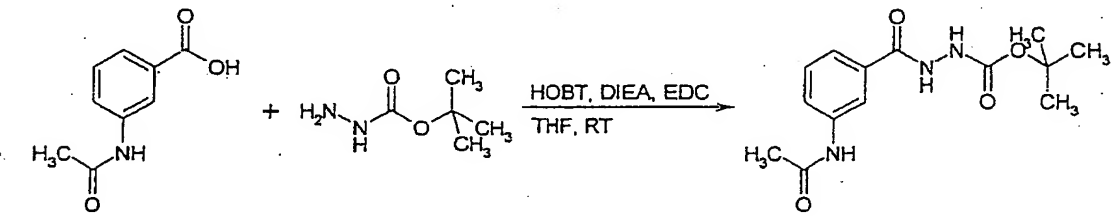
758 mg (84% of theory) of product are obtained starting from 1 g (3.2 mmol) of 5-(3-bromo-5-nitrophenyl)-4,4-dimethyl-2,4-dihydro-3*H*-pyrazol-3-one with 3.61 g (16 mmol) of tin dichloride dihydrate.

HPLC (method 3): R_t = 3.31 min

MS (EPIpos): m/z = 282 $(M+H)^+$

Example 11A

tert-Butyl 2-[3-(acetylamino)benzoyl]hydrazinecarboxylate



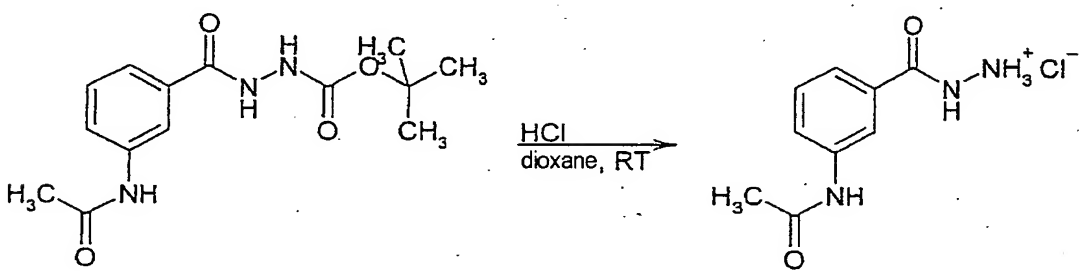
25.00 g (139.53 mmol) of 3-aminoacetylbenzoic acid are dissolved in 300 ml of THF (0.47 M solution). 20.74 g (153.48 mmol) of 1-hydroxy-1H-benzotriazole hydrate, 18.03 g (139.53 mmol) of *N,N*-diisopropylethylamine and 26.75 g (139.53 mmol) of N'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide x HCl are added to the solution. Subsequently, 18.44 g (139.53 mmol) of tert-butyl hydrazineformate are added, and the mixture is stirred at room temperature for 16 hours.

The solvent is removed and the residue is partitioned between equal parts of ethyl acetate and 1N hydrochloric acid. The organic phase is washed twice with 1N hydrochloric acid and twice with saturated sodium bicarbonate solution, during which part of the product precipitates as solid which is filtered off with suction, washed with ethyl acetate and dried in vacuo. The organic phase is dried over sodium sulfate and then filtered and concentrated. The residue is taken up in ethyl acetate, the resulting suspension is mixed with the same volume of diethyl ether, and the mixture is stirred at room temperature. After crystallization is complete, the product is filtered off with suction, washed with diethyl ether and dried in vacuo. The two product fractions are combined to result in 31.47 g (77% of theory) of product.

1H NMR (200 MHz, DMSO): δ = 1.43 (s, 9H), 2.06 (s, 3H), 7.28-7.58 (m, 2H), 7.69-7.85 (m, 1H), 8.02 (s, 1H), 8.90 (s, 1H), 9.98-10.27 (m, 2H).

Example 12A

2-[3-(Acetylamino)benzoyl]hydrazinium chloride



30.97 g (105.58 mmol) of tert-butyl 2-[3-(acetylamino)benzoyl]hydrazinecarboxylate are dissolved in 200 ml of dioxane (0.53 M solution), and 200 ml of 4 M hydrochloric acid in dioxane (800 mmol) are added. The mixture is stirred at room temperature for four days. The crystals which are separated out are filtered off with suction, washed with diethyl ether and dried in vacuo. 28.80 g (119% of theory) of product are obtained.

HPLC (method 10): R_t = 1.92 min

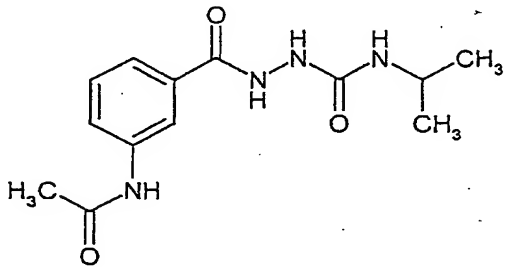
General method 6:

Synthesis of the hydrazinecarboxamides

1 equivalent of 2-[3-(acetylamino)benzoyl]hydrazinium chloride is introduced into dichloromethane (0.15 M solution) and stirred together with 2 equivalents of diisopropylethylamine and 1 equivalent of the appropriate isocyanate at room temperature for 16 hours. The resulting precipitate is filtered off with suction, washed with diethyl ether and dried in vacuo. The crude product is then immediately reacted further.

Example 13A

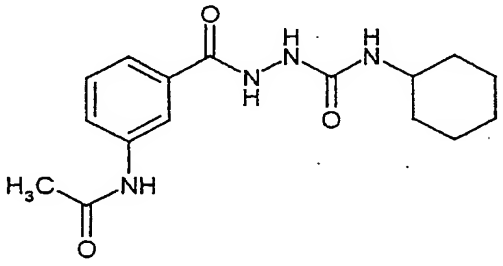
2-[3-(Acetylamino)benzoyl]-N-isopropylhydrazinecarboxamide



7.00 g (30.48 mmol) of 2-[3-(acetylamino)benzoyl]hydrazinium chloride are reacted with 7.88 g (60.96 mmol) of diisopropylethylamine and 2.59 g (30.48 mmol) of isopropyl isocyanate. The crude product is then immediately reacted further.
HPLC (method 3): R_t = 2.95 min

Example 14A

2-[3-(Acetylamino)benzoyl]-N-cyclohexylhydrazinecarboxamide

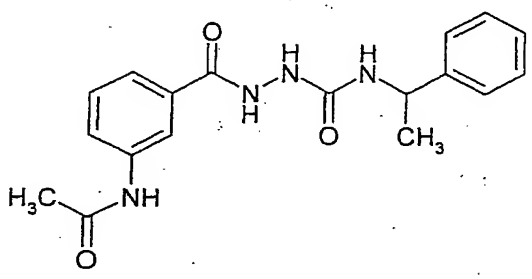


7.00 g (30.48 mmol) of 2-[3-(acetylamino)benzoyl]hydrazinium chloride are reacted with 7.88 g (60.96 mmol) of diisopropylethylamine and 3.82 g (30.48 mmol) of cyclohexyl isocyanate. The crude product is then immediately reacted further.

HPLC (method 3): R_t = 3.46 min

Example 15A

2-[3-(Acetylamino)benzoyl]-N-(1-phenylethyl)hydrazinecarboxamide



7.00 g (30.48 mmol) of 2-[3-(acetylamino)benzoyl]hydrazinium chloride are reacted with 7.88 g (60.96 mmol) of diisopropylethylamine and 4.49 g (30.48 mmol) of 1-phenylethyl isocyanate. The crude product is then immediately reacted further.

HPLC (method 3): R_t = 3.53 min

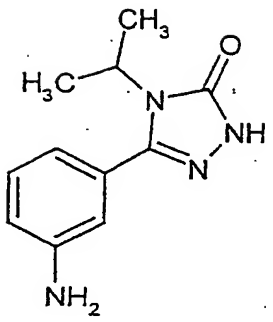
General method 7:

Synthesis of the 3-aminotriazolones

1 equivalent of the appropriate hydrazinecarboxamide is dissolved in 1N sodium hydroxide solution (0.16 M solution), and 6.15 equivalents of sodium hydroxide are added. The mixture is stirred at 100°C for 48 hours. The reaction solution is adjusted to pH 7 with hydrochloric acid, and the resulting precipitate is filtered off with suction, washed with water and dried in vacuo.

Example 16A

5-(3-Aminophenyl)-4-isopropyl-2,4-dihydro-3H-1,2,4-triazol-3-one

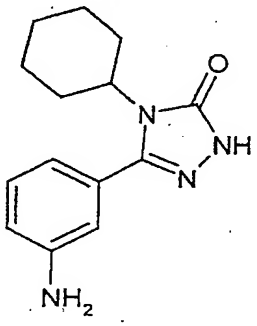


2.81 g (40% of theory) of product are obtained starting from 6.06 g (32.55 mmol) of 2-[3-(acetylamino)benzoyl]-N-isopropylhydrazinecarboxamide (crude) and 8.00 g (200.02 mmol) of sodium hydroxide in 200 ml of 1 N sodium hydroxide solution.

HPLC (method 3): R_t = 2.76 min

Example 17A

5-(3-Aminophenyl)-4-cyclohexyl-2,4-dihydro-3H-1,2,4-triazol-3-one

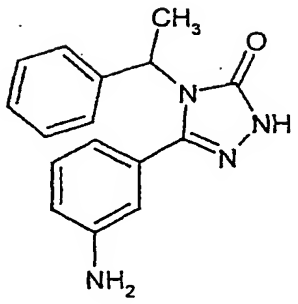


5.59 g (66% of theory) of product are obtained starting from 7.43 g (32.55 mmol) of 2-[3-(acetylamino)benzoyl]-N-cyclohexylhydrazinecarboxamide (crude) and 8.00 g (200.02 mmol) of sodium hydroxide in 200 ml of 1 N sodium hydroxide solution.

HPLC (method 3): R_t = 3.31 min

Example 18A

5-(3-Aminophenyl)-4-(1-phenylethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one



4.52 g (50% of theory) of product are obtained starting from 8.83 g (32.55 mmol) of 2-[3-(acetylamino)benzoyl]-N-(1-phenylethyl)hydrazinecarboxamide (crude) and 8.00 g (200.02 mmol) of sodium hydroxide in 200 ml of 1 N sodium hydroxide solution.

HPLC (method 3): $R_t = 3.35$ min

Preparation Examples

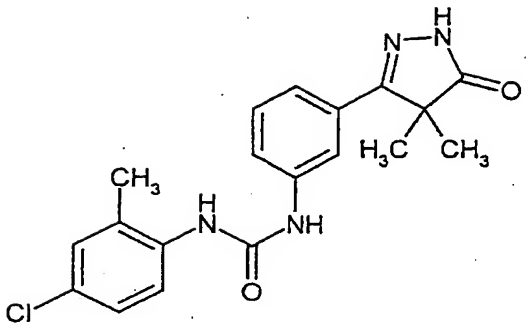
General method 8:

Synthesis of the ureas

0.24 mmol of the appropriate isocyanate are dissolved in 1 ml of ethyl acetate (0.2 ml of THF are also added where appropriate), and 0.2 mmol of the particular aniline are added. The mixture is stirred at room temperature overnight. The solvent is then removed, and the residue is taken up in DMSO or DMF and purified by RP-HPLC.

Example 1

N-(4-Chloro-2-methylphenyl)-N'-[3-(4,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)phenylurea



46.2 mg (0.28 mmol) of 4-chloro-2-methylphenyl isocyanate are mixed with a solution of 40 mg of 5-(3-aminophenyl)-4,4-dimethyl-2,4-dihydro-3*H*-pyrazol-3-one in 1 ml of ethyl acetate and 0.2 ml of tetrahydrofuran and stirred at room temperature overnight. The formation of a white precipitate is observed during this.

Workup: the reaction mixture is concentrated and the resulting residue is taken up in DMSO and then purified by RP-HPLC. 42 mg (58% of theory) of product are obtained as a white solid in this way.

m.p.: 226.8°C

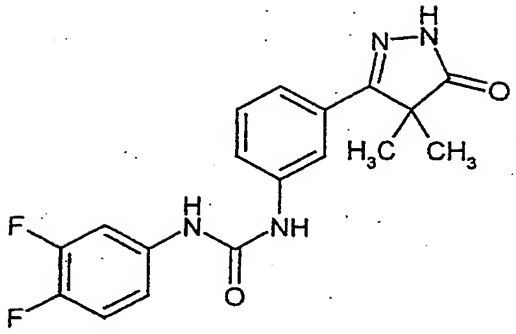
HPLC (method 3): $R_t = 4.33$ min

MS (ESIpos): m/z = 371 $(M+H)^+$

1H NMR (200 MHz, DMSO): δ = 1.37 (s, 6H), 2.25 (s, 3H), 7.21 (dd, 1H), 7.28 (d, 1H), 7.35-7.46 (m, 3H), 7.88 (d, 1H), 8.02 (s br, 1H), 8.11 (s br, 1H), 9.23 (s br, 1H), 11.54 (s br, 1H)

Example 2

N-(3,4-Difluorophenyl)-N'-[3-(4,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-phenyl]urea



42.7 mg (0.28 mmol) of 3,4-difluorophenyl isocyanate are mixed with a solution of 40 mg of 5-(3-aminophenyl)-4,4-dimethyl-2,4-dihydro-3*H*-pyrazol-3-one in 1 ml of ethyl acetate and 0.2 ml of tetrahydrofuran and stirred at room temperature overnight. The formation of a white precipitate is observed during this.

Workup: the reaction mixture is concentrated and the resulting residue is taken up in DMSO and then purified by RP-HPLC. 41.4 mg (59% of theory) of product are obtained as a white solid in this way.

m.p.: 226.7°C

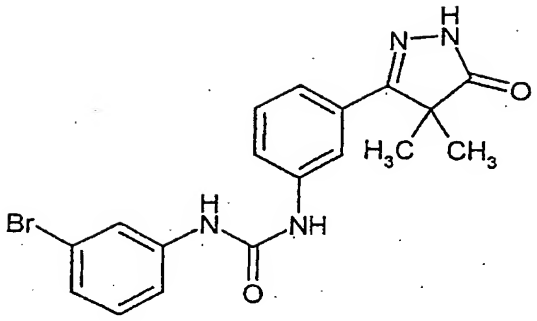
HPLC (method 3): R_t = 4.23 min

MS (ESIpos): m/z = 359 $(M+H)^+$

1H NMR (200 MHz, DMSO): δ = 1.38 (s, 6H), 7.13-7.17 (m, 1H), 7.28-7.46 (m, 4H), 7.66 (ddd, 1H), 8.06 (s br, 1H), 8.96 (s br, 2H), 11.54 (s br, 1H)

Example 3

N-(3-Bromophenyl)-N'-[3-(4,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl]urea



54.6 mg (0.28 mmol) of 3-bromophenyl isocyanate are mixed with a solution of 40 mg of 5-(3-aminophenyl)-4,4-dimethyl-2,4-dihydro-3*H*-pyrazol-3-one in 1 ml of ethyl acetate and 0.2 ml of tetrahydrofuran and stirred at room temperature overnight. The formation of a white precipitate is observed during this.

Workup: the reaction mixture is concentrated and the resulting residue is taken up in DMSO and then purified by RP-HPLC. 65 mg (82% of theory) of product are obtained as a white solid in this way.

m.p.: 236.9°C

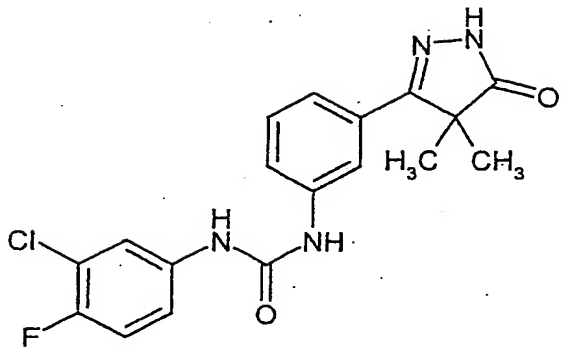
HPLC (method 3): R_t = 4.34 min

MS (ESIpos): m/z = 401 $(M+H)^+$

1H NMR (200 MHz, DMSO): δ = 1.38 (s, 6H), 7.15 (m, 1H), 7.25 (t, 1H), 7.32-7.46 (m, 4 H), 7.84 (s br, 1H), 8.06 (s br, 1H), 8.96 (s br, 2H), 11.55 (s, br 1H)

Example 4

N-(3-Chloro-4-fluorophenyl)-N'-[3-(4,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl]urea



47.3 mg (0.28 mmol) of 4-chloro-3-fluorophenyl isocyanate are mixed with a solution of 40 mg of 5-(3-aminophenyl)-4,4-dimethyl-2,4-dihydro-3*H*-pyrazol-3-one in 1 ml of ethyl acetate and 0.2 ml of tetrahydrofuran and stirred at room temperature overnight. The formation of a white precipitate is observed during this.

Workup: the reaction mixture is concentrated and the resulting residue is taken up in DMSO and then purified by RP-HPLC. 66.1 mg (90% of theory) of product are obtained as a white solid in this way.

m.p.: 257.5°C

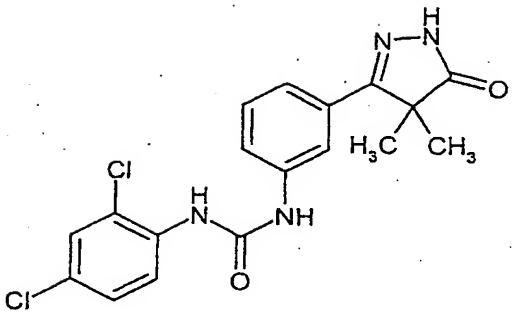
HPLC (method 3): R_t = 4.38 min

MS (ESIpos): m/z = 375 $(M+H)^+$

1H NMR (200 MHz, DMSO): δ = 1.38 (s, 6H), 7.31-7.47 (m, 5H), 7.79 (m, 1H), 8.06 (m, 1H), 8.94 (s br, 1H), 8.97 (s br, 1H), 10.99 (s br, 1H)

Example 5

N-(2,4-Dichlorophenyl)-N'-[3-(4,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl]urea



51.8 mg (0.28 mmol) of 2,4-dichlorophenyl isocyanate are mixed with a solution of 40 mg of 5-(3-aminophenyl)-4,4-dimethyl-2,4-dihydro-3*H*-pyrazol-3-one in 1 ml of ethyl acetate and 0.2 ml of tetrahydrofuran and stirred at room temperature overnight. The formation of a white precipitate is observed during this.

Workup: the reaction mixture is concentrated and the resulting residue is taken up in DMSO and then purified by RP-HPLC. 28.5 mg (38% of theory) of product are obtained as a white solid in this way.

m.p.: 242°C

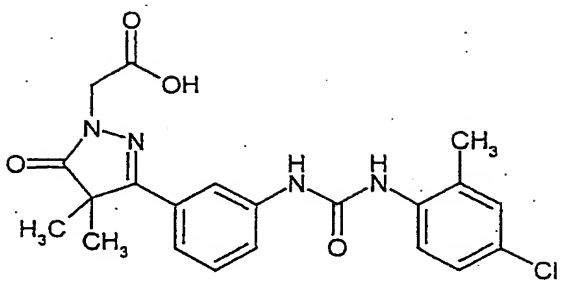
HPLC (method 3): R_t = 4.56 min

MS (ESIpos): m/z = 390 $(M)^+$

1H NMR (200 MHz, DMSO): δ = 1.48 (s, 6H), 7.22 (dd, 1H), 7.28-7.48 (m, 4H), 8.09 (m, 1H), 8.14 (s br, 1H), 8.27 (d, 1H), 9.32 (s br, 1H), 11.10 (s br, 1H)

Example 6

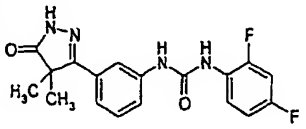
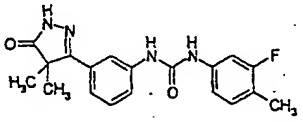
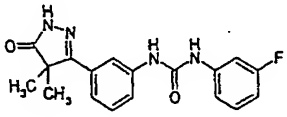
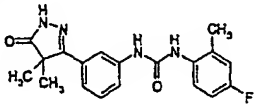
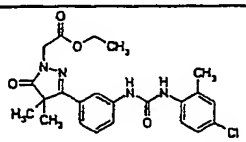
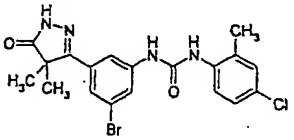
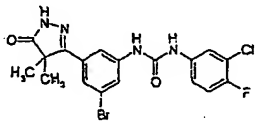
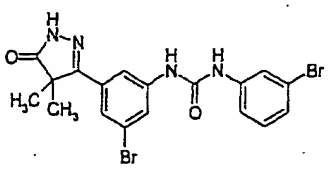
{3-[3-({[(4-Chloro-2-methylphenyl)amino]carbonyl}amino)phenyl]-4,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl}acetic acid

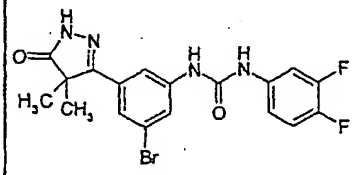
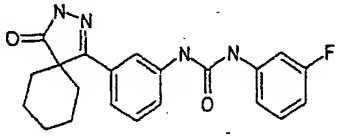


100 mg (0.22 mmol) of ethyl {3-[3-({[(4-Chloro-2-methylphenyl)amino]-carbonyl}amino)phenyl]-4,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl}acetate are dissolved in 2 ml of methanol and 1 ml of THF and, after addition of 1.7 ml of 1N sodium hydroxide solution, stirred at 50°C for 1 hour. Water is then added, and the mixture is extracted with ethyl acetate. The aqueous phase is acidified with hydrochloric acid and then extracted 3x with ethyl acetate. The combined organic extracts are dried over magnesium sulfate. The crude product, after filtration and removal of the solvent, is dried in vacuo and requires no further purification. 97 mg (quantitative) of product are obtained.

HPLC (method 3): $R_t = 4.35$ min

MS (ESIpos): m/z = 329 $(M+H)^+$

Example	Structure	MW	MS (ESI+) m/z	HPLC Rt[min]	HPLC method
7		358.35	359	4.19	3
8		354.38	355	4.35	3
9		340.36	341	4.21	3
10		354.38	355	4.2	3
11		456.93	474	4.66	3
12		449.73	449	4.71	3
13		453.70	453	4.69	3
14		480.16	479	4.71	3

Example	Structure	MW	MS (ESI+) m/z	HPLC Rt[min]	HPLC method
15		437.24	437	4.56	3
16		380.42	381	4.45	3

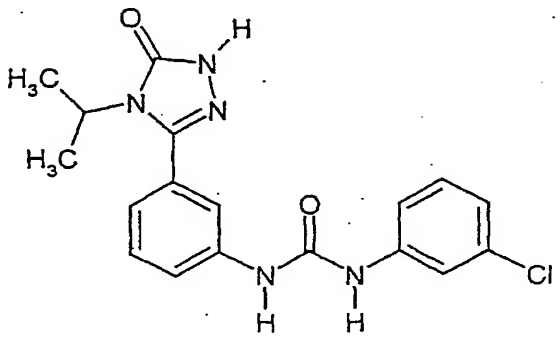
General method 9:

Ureas

1 equivalent of the aniline is introduced into THF (0.14 M solution) and mixed with 1 equivalent of the appropriate isocyanate. The solution is shaken at room temperature for 1 hour. The solvent is removed in vacuo and the product is purified by preparative HPLC (CromSil C 18, 250x30, flow rate: 50 ml/min, running time: 38 min, detection at 210 nm, gradient: 10% acetonitrile (3 min)->90% acetonitrile (31 min)-> 90% acetonitrile (34 min)-> 10% acetonitrile (34.01 min)).

Example 17

N-(3-Chlorophenyl)-N'-[3-(4-isopropyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)phenyl]urea



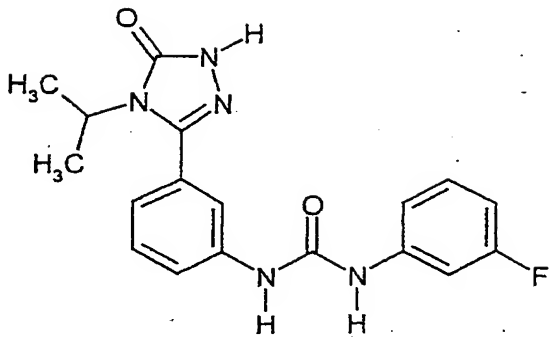
67.60 mg (66% of theory) of product are obtained starting from 60.00 mg (0.27 mmol) of 5-(3-aminophenyl)-4-isopropyl-2,4-dihydro-3H-1,2,4-triazol-3-one with 42.22 mg (0.27 mmol) of 3-chlorophenyl isocyanate.

HPLC (method 3): R_t = 4.22 min

1H NMR (200 MHz, d_6-DMSO): δ = 11.80 (s, 1H); 9.00 (d, 2H); 7.70 (s, 2H); 7.57-7.36 (m, 2H); 7.32-7.29 (m, 2H); 7.14-7.00 (m, 2H) 4.17-4.10 (m, 1H); 1.41 (d, 6H).

Example 18

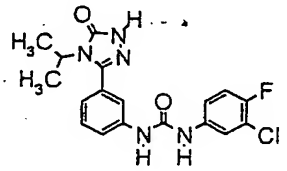
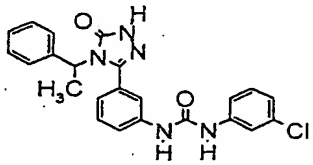
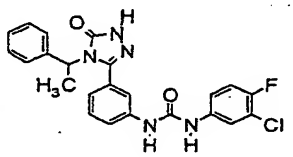
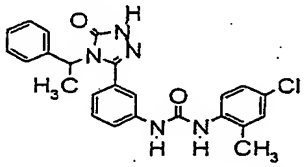
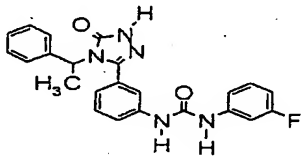
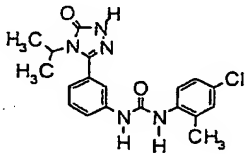
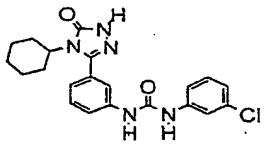
N-(3-Chloro-4-fluorophenyl)-N'-[3-(4-isopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl]urea

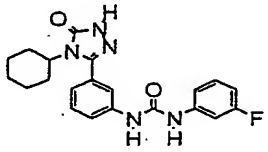
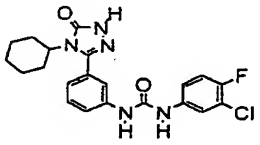


57 mg (33% of theory) of product are obtained starting from 150.0 mg (0.69 mmol) of 5-(3-aminophenyl)-4-isopropyl-2,4-dihydro-3H-1,2,4-triazol-3-one with 94.2 mg (0.69 mmol) of 3-chloro-4-fluorophenyl isocyanate.

HPLC (method 3): R_t = 4.12 min

1H NMR (200 MHz, d_6-DMSO): δ = 11.80 (s, 1H); 9.31 (d, 2H); 7.86-7.09 (m, 8H); 4.17-4.10 (m, 1H); 1.41 (d, 6H).

Example	Structure	MW	MS (ESI+) m/z	HPLC Rt[min]	HPLC method
19		389.82	390	4.25	3
20		433.90	434	4.58	3
21		451.89	452	4.6	3
22		447.92	448	4.64	3
23		417.44	418	4.42	3
24		385.85	386	3.76	5
25		411.89	412	4.58	3

Example	Structure	MW	MS (ESI+) m/z	HPLC Rt[min]	HPLC method
26		395.44	396	4.32	3
27		429.88	430	4.61	3

B. Assessment of the physiological activity

The *in vitro* effect of the compounds of the invention can be shown in the following assays:

Anti-HCMV (anti-human cytomegalovirus) cytopathogenicity tests

The test compounds are employed as 50 millimolar (mM) solutions in dimethyl sulfoxide (DMSO). Ganciclovir, foscarnet and cidofovir are used as reference compounds. After addition of in each case 2 µl of the 50, 5, 0.5 and 0.05 mM DMSO stock solutions to 98 µl portions of cell culture medium in row 2 A-H for duplicate determinations, 1:2 dilutions are carried out with 50 µl portions of medium up to row 11 of the 96-well plate. The wells in rows 1 and 12 each contain 50 µl of medium. In 150 µl of a suspension of 1×10^4 cells (human prepuce fibroblasts [NHDF]) were pipetted into each of the wells (row 1 = cell control) and, in rows 2-12, a mixture of HCMV-infected and uninfected NHDF cells (M.O.I. = 0.001 – 0.002), i.e. 1-2 infected cells per 1000 uninfected cells. Row 12 (without substance) serves as virus control. The final test concentrations are 250-0.0005 µM. The plates are incubated at 37°C/5% CO_2 for 6 days, i.e. until all the cells are infected in the virus controls (100% cytopathogenic effect [CPE]). The wells are then fixed and stained by adding a mixture of formalin and Giemsa's dye (30 minutes), washed with double-distilled water and dried in a drying oven at 50°C. The plates are then assessed visually using an overhead microscope (plaque multiplier from Technomara).

The following data can be acquired from the test plates:

CC_{50} (NHDF) = substance concentration in µM at which no visible cytostatic effects on the cells are evident by comparison with the untreated cell control;
EC_{50} (HCMV) = substance concentration in µM which inhibits the CPE (cytopathic effect) by 50% compared with the untreated virus control;
SI (selectivity index) = CC_{50} (NHDF) / EC_{50} (HCMV).

Representative in vitro data for the effects of the compounds of the invention are shown in Table A:

Table A

Example No.	NHDF CC50 [μM]	HCMV EC50 [μM]	SI HCMV
1	>5	0.5	>10
2	>20	0.5	>40
4	>10	0.4	>25
11	19.2	0.38	51
12	>14	2.1	>7
16	>31	1.9	>16
17	20	0.19	105
22	21	0.5	
25	31	0.3	
27	14	0.29	

The suitability of the compounds of the invention for the treatment of HCMC infections can be shown in the following animal models:

HCMV Xenograft Gelfoam® model

Animals:

3-4-week old female immunodeficient mice (16-18 g), Fox Chase SCID or Fox Chase SCID-NOD or SCID beige, are purchased from commercial breeders (Bomholtgaard, Jackson). The animals are housed under sterile conditions (including bedding and feed) in isolators.

Virus growing:

Human cytomegalovirus (HCMV), DavisSmith strain, is grown *in vitro* on human embryonic prepuce fibroblasts (NHDF cells). After the NHDF cells have been infected with a multiplicity of infection (M.O.I.) of 0.01, the virus-infected cells are harvested 5-7 days later and stored in the presence of minimal essential medium

(MEM), 10% fetal calf serum (FCS) with 10% DMSO at –40°C. After serial ten-fold dilutions of the virus-infected cells, the titer is determined on 24-well plates of confluent NHDF cells after vital staining with neutral red.

Preparation of the sponges, transplantation, treatment and evaluation:

Collagen sponges 1×1×1 cm in size (Gelfoam®; from Peasel & Lorey, order No. 407534; K.T. Chong et al., Abstracts of 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1999, p. 439) are initially wetted with phosphate-buffered saline (PBS), the trapped air bubbles are removed by degassing, and then stored in MEM + 10% FCS. 1×10^6 virus-infected NHDF cells (infection with HCMV Davis M.O.I. = 0.01) are detached 3 hours after infection and added in a drop of 20 µl of MEM, 10% of FCS, to a moist sponge. 12-13 hours later, the infected sponges are incubated with 25 µl of PBS / 0.1% BSA / 1 mM DTT with 5 ng/µl basic fibroblast growth factor (bFGF). For the transplantation, the immunodeficient mice are anesthetized with Avertin, the fur on the back is removed using a dry shaver, the epidermis is opened 1-2 cm, unstressed and the moist sponges are transplanted under the dorsal skin. The surgical wound is closed with tissue glue. 24 hours after the transplantation, the mice are treated with substance orally three times a day (7.00 h and 14.00 h and 19.00 h) for a period of 8 days. The dose is 7 or 15 or 30 or 60 mg/kg of body weight, the volume administered is 10 ml/kg of body weight. The substances are formulated in the form of a 0.5% strength Tylose suspension with 2% DMSO. 9 days after transplantation and 16 hours after the last administration of substance, the animals are painlessly sacrificed and the sponge is removed. The virus-infected cells are released from the sponge by collagenase digestion (330 U/1.5 ml) and stored in the presence of MEM, 10% fetal calf serum, 10% DMSO at –140°C. Evaluation takes place after serial ten-fold dilutions of the virus-infected cells by determining the titer on 24-well plates of confluent NHDF cells after vital staining with neutral red. The number of infectious virus particles after the substance treatment compared with the placebo-treated control is determined.

C. Exemplary embodiments of pharmaceutical compositions

The compounds of the invention can be converted into pharmaceutical preparations in the following ways:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of corn starch (native), 10 mg of polyvinylpyrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of active ingredient, lactose and starch is granulated with a 5% strength solution (m/m) of the PVP in water. The granules are then dried and mixed with the magnesium stearate for 5 min. This mixture is compressed using a conventional tablet press (see above for format of the tablet). A guideline for the compressive force used for the compression is 15 kN.

Suspension which can be administered orally:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

10 ml of oral suspension are equivalent to a single dose of 100 mg of the compound of the invention.

Production:

The Rhodigel is suspended in ethanol, and the active ingredient is added to the suspension. The water is added while stirring. The mixture is stirred for about 6 h until the swelling of the Rhodigel is complete.